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HISTOLOGIC AND BACTERIOLOGIC INVESTIGATIONS ON PATIENTS WITH PULMONARY RESECTION TREATED WITH ANTIBIOTICS

BY

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INTRODUCTION

In the treatment of pulmonary tuberculosis, chances for resection have greatly been increasing mostly because the disease can be controlled with specific drugs acting on the disease process, before the operation. Medical treatment given sufficiently long after operation is likely to secure positive results. When considering the indications for resection and especially when planning the extent of resection it is naturally important to know the influence of medical treatment on the process. In addition to the resistance determinations, the purpose of this study is to examine the influence of chemotherapy on the histologic picture of the disease.

We wish to extend our sincere thanks to Professor Jorma Pätiälä, M.D., for his keen interest in our work and for his valuable suggestions concerning the problems of pulmonary tuberculosis. We also wish to thank Dr. Lars Hjelt, M.D., for his expert knowledge in the evaluation of histologic specimens and Dr. Eljas Brander for his advice in bacteriologic examinations.

METHODS AND CLINICAL DATA OF THE PATIENTS

METHODS

The series consisted of 34 patients with pulmonary tuberculosis resected in the III Surgical Clinic in the years 1955—1956 (Turunen). From resected lungs and lymph nodes, 99 biopsy specimens were taken in all. If possible, they were taken from the wall of the cavity, from some other focus in the lung, and from the hilus glands of each patient. Histological preparations were made from all specimens using hematoxylin — eosin and Weigert's resorcin — fuchsin staining methods. Likewise, tubercle and other ordinary bacterial cultures were made from all specimens. From 28 specimens, resistance of tubercle bacilli to Streptomycin, INH and PAS was also determined. For the tuberculosis examination, the excised specimens were pulverized in a mortar with physiological saline to form an even suspension. After centrifugation and treatment with one per cent hydrochloric acid for 12 hours, each precipitate was inoculated into five test tubes containing Löwenstein-Jensen culture medium. Before the treatment of the specimens with hydrochloric acid plate cultures were made on the usual culture medium used in routine bacteriological work (Blood agar, McLeod and Drigalski agar). For resistance examination, the specimens were pulverized in a mortar and suspended with saline. Löwenstein-Jensen culture medium was used for these cultures, too.

CLINICAL DATA

The age and sex of the patients can be seen in Table 1.

The number of males and females was approximately the same. The youngest patient was 16, and the oldest 54 years old. Of the

TABLE 1

AGE AND SEX OF THE PATIENTS

	11—20 Years	21—40 Years	Over 40 Years	Total Number of Patients
Female	3	12	3	18
Male	—	12	4	16
Totals	3	24	7	34

patients, 79 per cent were under 40 years of age. This age limit has to be noted because Medlar, *e.g.*, reported that most of the patients under 40 years of age have progressive primary tuberculosis reinfection prevailing among patients over 40.

Table 2 shows the duration of the disease among the patients, grouped according to their ages.

TABLE 2

DURATION OF THE DISEASE BEFORE RESECTIONAL TREATMENT

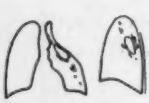
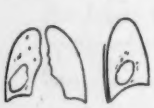
Age of the Patient	Duration of the Disease			
	1—5 Years	5—10 Years	Over 10 Years	Totals
11—20 years ..	2	1	—	3
21—40 years ..	12	10	2	24
Over 40 years..	3	2	2	7
Totals	17	13	4	34

As can be seen in Table 2, the duration of the disease was five years or more among half of the patients. Among the other half it varied from one to five years. The series included no case with a fresh process of the disease which could have been operated after fairly short medical treatment.

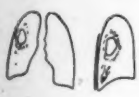
Table 3 illustrates the most important clinical findings, and the treatment given before resection. The site and the extension of the lung process was drawn on the basis of roentgenological and resectional findings. In addition, ESR, the occurrence of tubercle bacilli in sputum and bronchoscopy findings are also given.

TABLE 3

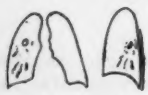
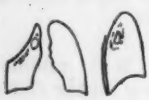
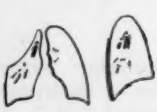
HISTORY AND CLINICAL DATA OF THE PATIENTS

No.	Picture	ESR	Sputum Staining	Bronchoscopy	Earlier Treatment	Resection	No.
1.		8	—	Tuberculous ulcerations in bronchus of middle lobe	Pneumothorax	Upper lobe resection on the right side	11.
2.		14	+	0	Pneumothorax	Upper lobe resection on the right side	12.
3.		10	+	0	Thoracoplasty	Upper lobe resection on the right side	13.
4.		30	+	Irritation in bronchus of middle lobe	Pneumoperitoneum	Middle and lower lobe resection on the right side	14.
5.		3	—	Irritation in bronchus of right upper lobe	Pneumothorax	Apicoposterior segmental resection of the upper lobe on the right side	15.
6.		29	+	0	Thoracoplasty	Pneumonectomy on the left side	16.
7.		35	+	0	Conservative	Pneumonectomy on the right side	17.
8.		13	—	0	Thoracoplasty	Upper lobe resection on the left side	18.
9.		30	+	0	Pneumothorax	Pneumonectomy on the left side	19.
10.		30	+	Tuberculous ulcerations in bronchus of right upper lobe	Thoracoplasty	Pneumonectomy on the right side	20.

(Conten.)

No.	Picture	ESR	Sputum Staining	Bronchoscopy	Earlier Treatment	Resection
11.		7	—	0	Conservative	Upper lobe resection and apical segmental resection of the lower lobe on the right side
12.		38	+	Irritation in left main bronchus	Pneumolysis	Upper lobe resection and apical segmental resection of the lower lobe on the left side
13.		6	—	0	Conservative	Upper and middle lobe resection on the right side
14.		14	+	Irritation in bronchus of right upper lobe	Conservative	Upper lobe resection on the right side
15.		4	+	0	Conservative	Apicoposterior segmental resection of the upper lobe on the right side
16.		7	—	0	Pneumo-peritoneum	Pneumonectomy on the left side
17.		48	—	Irritation in bronchus of right upper lobe	Conservative	Upper and middle lobe resection and apical segmental resection of the lower lobe on the right side
18.		36	+	0	Conservative	Apicoposterior segmental resection of the upper lobe on the right side
19.		10	—	Irritation in bronchus of left upper lobe	Conservative	Upper lobe resection and apicoposterior segmental resection of the lower lobe on the left side
20.		23	+	Irritation in right main bronchus	Pneumo-peritoneum	Pneumonectomy on the right side

(Conten.)

No.	Picture	ESR	Sputum Staining	Bronchoscopy	Earlier Treatment	Resection
21.		2	—	Stenosis in bronchus of right upper lobe	Conservative	Upper lobe resection on the right side
22.		5	—	0	Conservative	Lower lobe resection on the left side
23.		6	+	0	Thoraco-plasty	Upper lobe resection on the right side
24.		4	+	0	Thoraco-plasty	Upper lobe resection on the right side
25.		12	—	Irritation in bronchus of right upper lobe	Thoraco-plasty	Upper and middle lobe resection and apical segmental resection on the lower lobe on the right side
26.		4	—	0	Pneumo-peritoneum	Middle lobe resection on the right side
27.		50	+	0	Pneumo-thorax	Pneumonectomy on the right side
28.		7	—	0	Conservative	Upper lobe resection on the right side
29.		11	+	0	Pneumo-thorax	Upper lobe resection and apical segmental resection of the lower lobe on the right side
30.		32	+	0	Thoraco-plasty	Pneumonectomy on the left side

(Conten.)

No.	Picture	ESR	Sputum Staining	Bronchoscopy	Earlier Treatment	Resection
31.		8	—	0	Pneumothorax	Upper lobe resection on the right side
32.		22	+	Irritation in bronchus of left lower lobe	Thoracoplasty	Pneumonectomy on the left side
33.		3	+	0	Pneumoperitoneum	Upper lobe resection on the right side
34.		14	+	0	Pneumoperitoneum Monaldi Thoracoplasty	Pneumonectomy on the left side

It can be seen in Table 3, that 20 patients (59 per cent) showed tubercle bacilli in sputum immediately before operation. However, the culture made from sputum had at least once been positive with each patient. Table 3 shows further that the disease was rather advanced among most patients. A cavity diagnosed in an earlier roentgenological examination was almost always present. Among eight patients, the disease affected both lungs. In bronchoscopy, only three patients showed bronchotuberculosis. In addition, irritation in bronchi was observed among a few patients, which was obviously due to the pus passing the bronchi (cf. Medlar). On admission, the process of the disease among the patients was so advanced that the resections had to be extensive. The number of pneumectomies was ten. There were 11 resected upper lobes, the apical segment of lower lobe, too, being resected from four patients. Resection of a segment only was performed on three patients.

Table 4 shows resectional indications of the patients.

TABLE 4

RESECTIONAL INDICATIONS

Thoracoplasty failure	10
Pneumothorax failure	7
Bronchial tuberculosis	3
Bronchial ectasia and cavity	3
Destroyed lung	5
Tuberculoma	1
Thick-walled cavity	2
Cavity of lower and middle lobes	3

As can be seen in Table 4 resection was performed on 17 patients with previous failed collapse therapy. Among other patients, the localization, type and extent of the process suggested primary resectional treatment.

BACTERIOLOGICAL INVESTIGATIONS

EARLIER INVESTIGATIONS

As Canetti stated there are two main bacteriological problems: the sterilization of the lesion and the changes in the resistance of bacilli caused by chemotherapy. In tuberculous lesions, the degree of sterilization is different in cavities and in closed caseous necrosis. Most open cavities contain bacilli even after chemotherapy. This has also been emphasized, *i.a.*, by Medlar in several connections. In similar case, positive cultures were obtained in 6 to 36 per cent according to Canetti, and in 13 per cent according to Medlar. Necrotic tissue often contains bacilli (Medlar). The number of bacilli is not, however, correlated to the size of necrosis because they can be found abundantly in small necroses, too. Most abundant bacilli occur in open cavities, in caseous necrosis they are less frequent, sometimes they do not grow at all. According to Canetti, chemotherapy does not much affect these bacilli. Only few bacilli were found by Medlar in epithelioid tubercles. Dubos paid attention to the bacilli visible in smears from caseous necrosis which, however, do not grow. He supposed that though these bacilli are often considered dead their inability to grow might be due to poor culture technic. The Guinea-pig test is better than culture when deciding whether these bacilli are dead or not.

CULTURE RESULTS

Table 5 illustrates results of tuberculosis cultures made from resected specimens. Groups were formed according to the origin of specimens. — The other usual bacteriological cultures were all negative, which corresponds to the observation made by Medlar *et al.*

TABLE 5

RESULTS OF TUBERCULOSIS CULTURES

Preparation	Positive	Negative	Totals
Wall of cavity	20	7	27
Other focus	20	16	36
Hilus gland	9	17	26
[1]Others	5	5	10
Totals	54	45	99

[1] The specimens taken from bronchi, from thickened and hardened pleura and from intrathoracic sebaceous glands.

Of the cultures, 54.5 per cent were positive, the corresponding figure in Medlar's study being 40 per cent. Culture results in different groups roughly correspond to earlier observations. Relatively frequent positive findings from hilus glands (52.9 per cent) are of special interest. Similar percentage was obtained by Pätiälä *et al.*

ANTIBIOTIC TREATMENT AND ITS INFLUENCE ON CULTURE RESULTS

The patients were administered Streptomycin, PAS and INH, and three patients were given Conteben. The treatment among all patients was combined, as three patients only were not given INH. The failure of antibiotic treatment frequently indicated the resection. Table 6 shows the duration of antibiotic treatment and culture results.

TABLE 6

DURATION OF ANTIBIOTIC TREATMENT AND CULTURE RESULTS

Time	Patients	Preparations	Positive Cultures	Negative Cultures
Under 4 months..	3	11	1	10
4— 7 months ..	9	23	15	8
7—12 months ..	10	27	15	12
12—24 months ..	8	26	17	9
Over 24 months..	4	12	6	6
Totals	34	99	54	45

Most of the patients were treated chemotherapeutically over six months, the cultures still remaining positive. The number of positive culture results in different groups was approximately the

same irrespective of the duration of the treatment. Auerbach *et al.* also reported that there is no correlation between the occurrence of living bacilli in resected specimens and antibiotic treatment.

SENSITIVITY DETERMINATIONS

Sensitivity of tubercle bacilli to the commonly used chemotherapeutics, Streptomycin, INH and PAS was determined in 28 specimens all taken from different parts of the lungs of 11 patients. The results can be seen in Table 7, in which increasing sensitivity is marked with +, ++ and +++. At Streptomycin, + indicates no growth in culture medium containing 100 μ/ml, ++ no growth in concentration 10 μ/ml, and +++ no growth in 1 μ/ml. The corresponding figures with INH are 10;1 and 0.2 μ/ml, and with PAS 10;1 and 0.1 μ/ml. If growth was observed in all cultures, resistance is indicated with R.

TABLE 7

SENSITIVITY OF TUBERCLE BACILLI TO STREPTOMYCIN, INH AND PAS

	+++	++	+	R
Streptomycin..	10	6	11	1
INH	9	5	9	5
PAS	5	3	10	10

It can be seen in Table 7 that strains were least resistant to Streptomycin, and most resistant to PAS, which was previously often used in home treatment. The results of sensitivity examination will be discussed later in connection with pathological investigations.

PATHOLOGICAL INVESTIGATIONS

EARLIER STUDIES

The changes in patho-anatomical picture of pulmonary tuberculosis caused by chemotherapy greatly depend on the stage of the disease at the beginning of the treatment.

On the basis of pathological finding, Medlar divides the development of pulmonary tuberculosis into five stages. Original lesion is lobular pneumonia with no epithelioid tubercles or giant cells. At the next stage, lobular pneumonia can still be established with neutrophilic and monocytic infiltration. Lymphocytes are also found. At the third stage, inflammatory cells are disappearing. Clear neutrophilic infiltration is, however, seen here and there. In some interlobar septa, the connective tissue is thickened. At the fourth stage, clear necrosis with strongly fibrotic surrounding capsule is established. A bronchus with affected mucosa frequently leads to the necrosis. At the fifth stage, the capsule round the necrosis can be seen more clearly. Calcium and extremely strong fibrosis in the capsule is encountered. In the necrosis inside the capsule, a destroyed bronchus may be recognisable. After the necrosis of the fifth stage has emptied itself through the bronchus a cavity is established.

The original lesion, *i.e.*, lobular pneumonia can thus by resolution be completely cured, or it can develop into a tubercle and then be cicatrized. On the other hand, the lesion can develop into necrosis or a cavity, as has been described above.

According to Canetti, lobular pneumonia called by him recent tuberculous alveolitis can often be completely cured with medical treatment. This form of tuberculosis does not often occur in the patients selected for resection. In this type of lesion characterized

also by an increase of bacilli the influence of chemotherapy is both curative and preventive. Tørning also mentioned that the influence of chemotherapy is greatest upon fresh, not necrotic lesions. On the other hand, necrosis often occurs at a very early stage, even before the disease is clinically established. Therefore chemotherapy cannot always prevent the development of necrosis though it can prevent its progress.

Canetti mentioned that caseous necrosis is more resistant to chemotherapy. It is true that part of fresh caseous necroses are possibly changed by chemotherapy into collagenous tissue, but the treatment fails in extensive old foci. It can, however, prevent the liquefaction of caseous necroses. Long-time chemotherapy might also extend to cavities, but Medlar and Iwasaki do not believe that they would be cured. Changes in specific cellular metaplasia, *i.e.*, in epithelioid and giant cells and in their occurrence are extremely important signs of the influence of chemotherapy. Canetti greatly evaluates them. According to him, a paradoxical phenomenon is often observed in tuberculous lungs treated chemotherapeutically: occasional rise of cellular metaplasia. These changes are not frequent in the lung not treated chemotherapeutically, but occur abundantly as the result of chemotherapeutic treatment. Metaplastic cells are then of more various structure and appearance, and they are grouped in a different way. The giant cells, *e.g.*, are often of foreign body type. Denst also paid attention to the great number and various forms of giant cells. According to Canetti, experimental studies, however, show that the occurrence of these phenomena is not paradoxical, they are related to bacteriolysis. The increase of metaplasias is influenced by chemical agents. Accordingly, these changes well reflect the influence of chemotherapy.

On the basis of what has been written above, it can be established that the histologic picture of the tuberculous lung treated with antibiotics is not always the same. There are, however, typical changes, such as the small number of fresh pneumonias, decrease of perifocal inflammation (*i.a.*, Auerbach), the small number of tubercles (*i.a.*, Walner *et al.*), and strongly increased cellular metaplasia.

HISTOLOGIC OBSERVATIONS

Table 8 shows the results of the investigation including the clinical observations, macroscopic picture of resected lung, tuberculosis cultures and facts indicating antibiotic influence in histologic picture.

With regard to histologic changes indicating antibiotic influence a few important criteria were taken into the table: The pneumonia in the table refers to fresh lobular tuberculous pneumonia as described, *e.g.*, by Medlar and Canetti. The amounts of inflammatory cell infiltrations are marked +, ++ and +++, + indicating occasional small accumulation of inflammatory cells. Inflammatory cell infiltration is mononuclear unless there is a letter L indicating a noticeable occurrence of polymorphonuclear inflammatory cells. The same method has been used to show the size of the cavity, + means that the diameter of the cavity is less than ½ cm, +++ indicating the diameter of several centimetres. As to epithelioid tubercles, + indicates that an epithelioid tubercle has been found somewhere in the preparation, ++ refer to 1—2 tubercles, and +++ to great numbers of these lesions. The same method has been used correspondingly as to epithelioid cells. In the group of giant cells, + indicates 1—2, ++ 2—5, and +++ several cells. Metaplastic cells among this group are shown with a letter P. Macroscopical finding in the table refers to the description of the resected lung made by the surgeon. The evaluation of the degree of antibiotic influence has partly been based on the criteria established in Table 8, partly on the subjective conception.

It can be seen in Table 8 that the influence of the chemotherapy was favourable (++ or +++) in 32 specimens, less favourable (+) in 8 specimens. No influence could be observed in 59 specimens. The different specimens of the same patient varied a little as to the influence of the treatment, but none of the three groups showed markedly favourable results. Neither could relationship be observed between the duration of antibiotic treatment and the influence observed histologically.

Figures 1—12 throw further light on the histologic evaluations presented in Table 8.

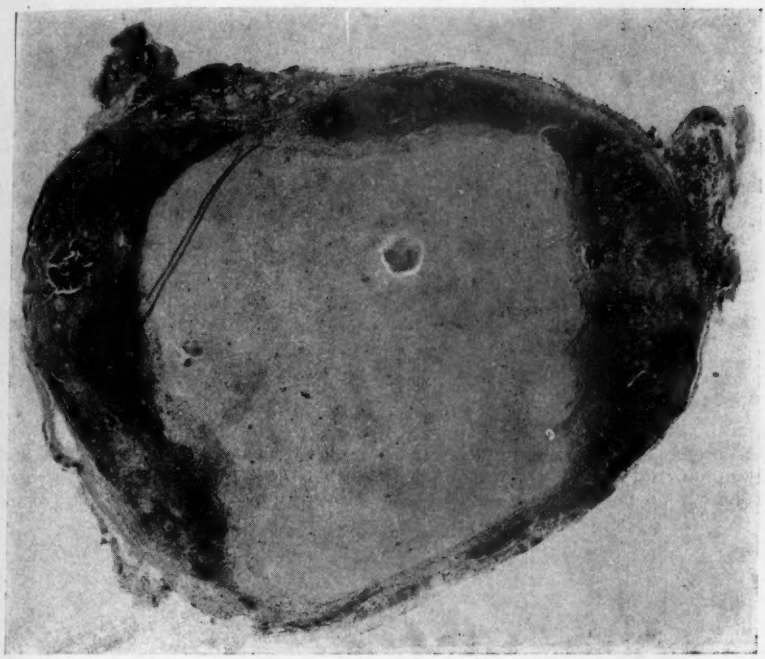


Fig. 1. — Lymph node. Case 27.

Extensive caseous necrosis in the middle of lymph node, and fresh epithelioid tubercles in periphery embedded in lymphatic tissue. Caseous necrosis is surrounded by connective fibrosis. × 50.

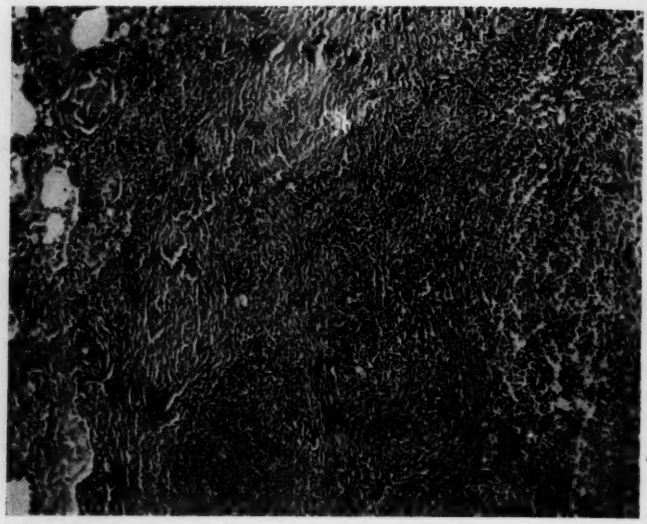


Fig. 2 — Wall of cavity. Case 4.

Cavity on the right surrounded by the area of epithelioid and giant cells and lymphocytes. Clear fibrosis in the middle of the wall. Strong inflammatory and tuberculous changes in periphery. Spread of the process into pulmonary tissue can also be seen. × 100.

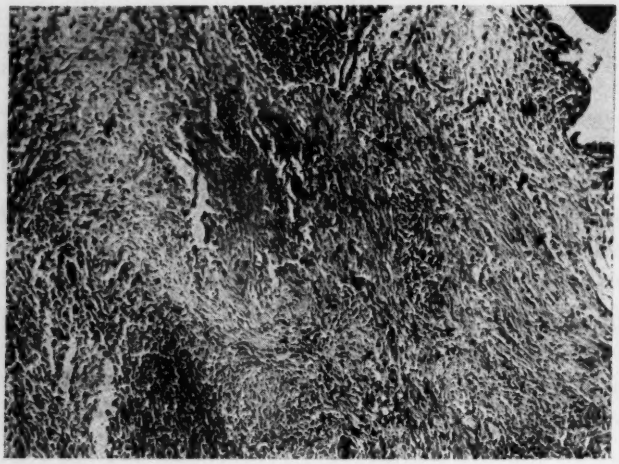


Fig. 3. — Other focus. Case 4.

Strong inflammatory and specific tuberculous changes in the wall of bronchus. × 100.

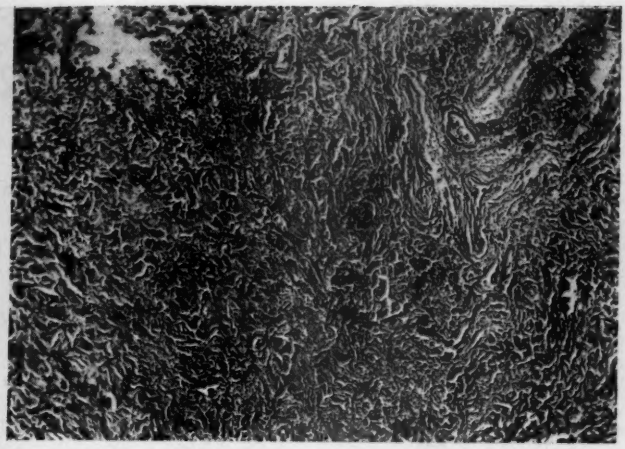


Fig. 4. — Wall of cavity. Case 21.

Completely fibrotic wall of cavity with no specific changes established. × 100.

Fig. 5. — Lymph node. Case 9.

Tubercles in a lymphatic node with connective tissue formation in periphery. Numerous accumulations of epithelioid cells, tubercles and several atypical giant cells can also be observed. × 100.

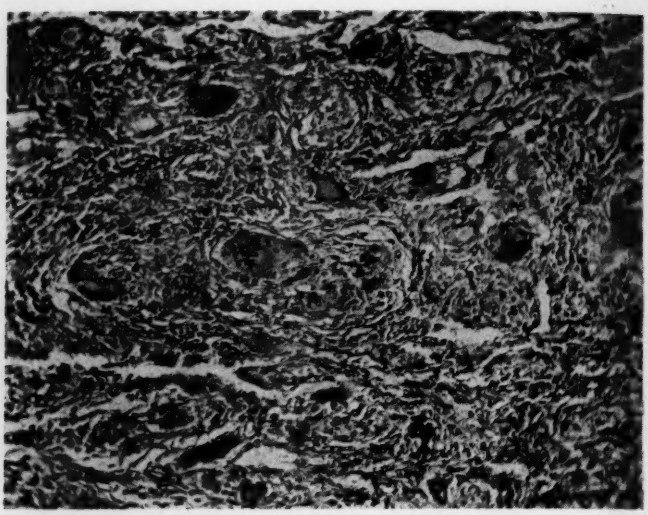


Fig. 6. — Other focus. Case 11.

Fibrotic lung with no necrotic areas to be seen. Many multinucleated giant cells. × 200.

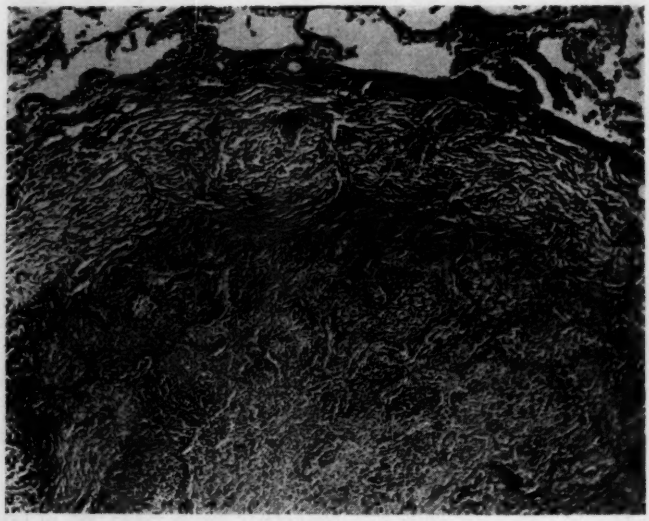


Fig. 7. — Other focus. Case 1.

Limited tubercle surrounded by hick connective tissue capsule. Giant cells in periphery. × 50.

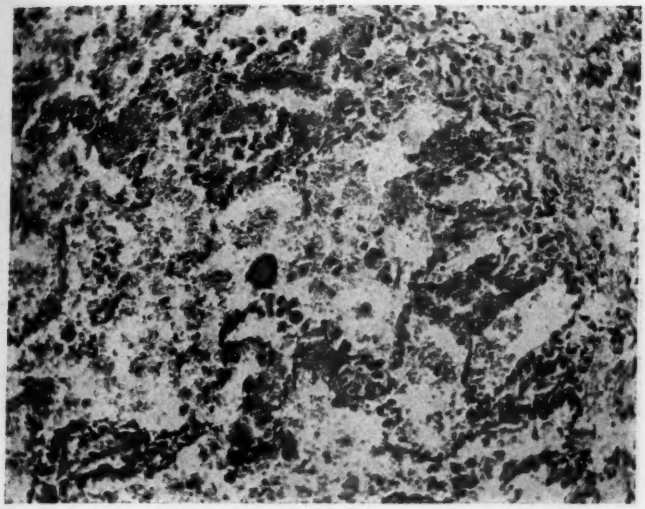


Fig. 8. — Other focus. Case 7.

Giant cell pneumonia with giant cells in alveoli. Few inflammatory cells, but erythrocytes in alveoli in addition to giant cells. × 300.

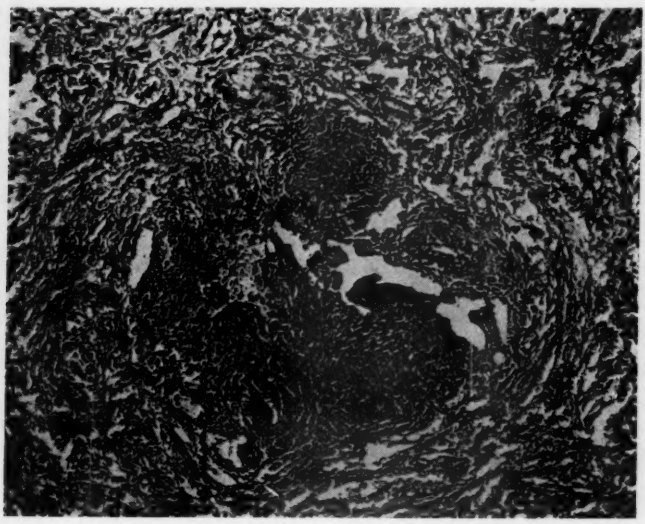


Fig. 9. — Other focus. Case 1.

Fibrotic lung in a placid state with strong inflammation round bronchus. Apparently endobronchial dissemination. × 100.

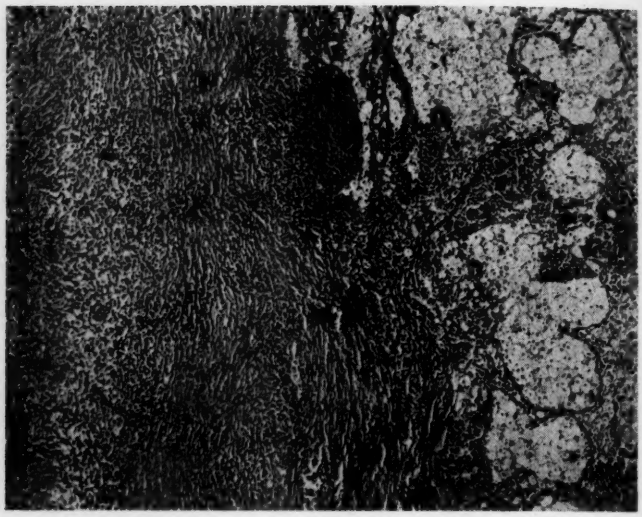


Fig. 10. — Wall of cavity. Case 13

Fibrosis on the wall of cavity with strong lymphocytic infiltration penetrating the wall. No giant cells in the picture. × 100.

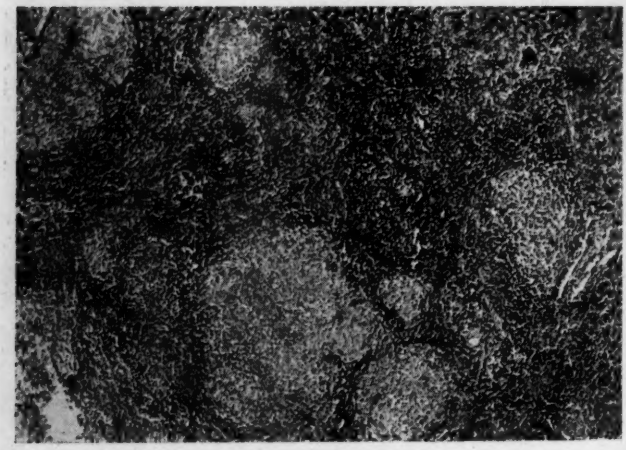


Fig. 11. — Lymph node. Case 6.

Irregularly limited conglomerate tubercles in lymph node. No giant cells. × 100.

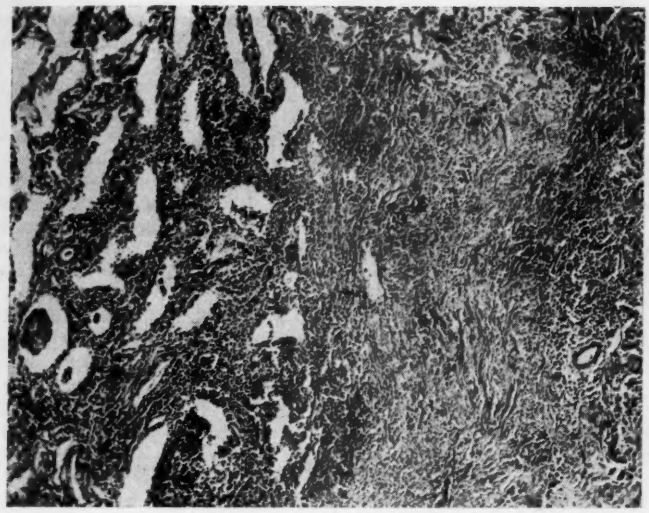


Fig. 12. — Wall of cavity. Case 4.

From the wall of cavity strong inflammation goes out to periphery with fresh tuberculous and pneumonic changes. × 100.

TABLE 8 CLINICAL OB

RESULTS OF TUBERCLE CULTURES COMPARED WITH HISTOLOGIC FINDINGS, AND THE INFLUENCE OF

No.	Macroscopical Findings	Duration of Treatment	Sputum Staining	Specimen
1.	Upper lobe with cavity in apicoposterior segment. Lung otherwise not affected	48 months	—	Hilus gland Tubercle of anterior segment Wall of cavity
2.	Upper lobe with egg sized cavity in apical segment. Lung otherwise not affected	6 months	+	Ectatic bronchus Wall of cavity Hilus gland
3.	Atelectatic upper lobe. Several fingertip-sized cavities in parenchyma	9 months	+	Wall of cavity Calcareous focus
4.	Reduced lower lobe with cavities. Middle lobe with tuberculoma and small cavities	48 months	+	Wall of cavity Focus of middle lobe Hilus gland
5.	Apicopostal segment with full-sized cavity and tuberculoma	5 months	—	Wall of cavity Tuberculoma
6.	Cavity in the apex. Lower lobe with fibrotic apical segment and a few foci	36 months	+	Wall of cavity Focus of lower lobe Hilus gland
7.	Apical segment of lower lobe with cavity extending into upper lobe. Foci in all lobes	15 months	+	Wall of cavity Focus of lower lobe Hilus gland Bronchus of lower lobe
8.	Atelectatic left upper lobe. Cavity in the apex	12 months	—	Wall of cavity Apical focus Hilus gland
9.	Upper lobe with large cavity. Apical segment of lower lobe with cavity. Numerous foci in lower lobe	24 months	+	Wall of cavity, lower lobe Wall of cavity, upper lobe Focus of upper lobe Hilus gland
10.	Upper lobe with cavity and numerous foci. Numerous tuberculomas in middle and lower lobes	12 months	+	Wall of cavity Middle lobe Focus of lower lobe Hilus gland
11.	Upper lobe with two large cavities. Glands round bronchus	20 months	—	Wall of cavity Focus of lower lobe Extensive bronchus Hilus gland
12.	Atelectatic upper lobe. Apical segment of lower lobe with numerous foci	13 months	+	Tuberculoma Stump of bronchus Hilus gland
13.	Shrunken upper lobe with cavity. Bronchial ectasies in middle lobe	4 months	—	Wall of cavity Thickened and hardened pleura Hilus gland
14.	Right atelectatic upper lobe with small cavity	7 months	+	Tuberculoma Caseous necrosis Atelectasis of upper lobe
15.	Upper lobe with tuberculoma in apicoposterior segment. Surrounding foci	4 months	+	Tuberculoma Tubercles
16.	Cavity in left apex. Process extends into the lower lobe	1½ months	—	Wall of cavity Fibrosis of upper lobe Bronchus of lower lobe Hilus gland

CLINICAL OBSERVATIONS

INFLUENCE OF CHEMOTHERAPY ON PULMONARY TISSUE OBSERVED HISTOLOGICALLY AND MACROSCOPICALLY

Culture	Pneumonia	Inflammatory Infiltration	Cavity	Necrosis	Tubercles	Epithelioid Cells	Giant Cells	Fibrosis	Influence
—	—	—	—	—	+	+++	++	+++	++
—	—	++	—	+++	+	+++	+++P	++	++
+	—	++L	++	+++S	++	+	++P	+++	+
+	—	+	+++	+	—	+++	++P	+++	++
+	No tuberculous changes								
—	No tuberculous changes								
+	—	++L	+++	+	+++	+	+	++	—
—	—	+	—	—	—	+	—	+++	E
+	+	+++	+	+++	+++	+	+	+++	—
—	+	+++L	—	+++S	+++	+	+	++	—
—	—	—	—	+	+++	+++	+	++	—
+	—	++L	+++	++	+++	+	+	++	+
+	—	++	—	++S	—	++	++	++	++
+	—	++	+++	+++	++	+	+	+++	+
—	No tuberculous changes								
—	No tuberculous changes								
+	—	++	++	+++	+++	++	+	+++	—
+	—	++	—	++	+	+++	+++P	+++	+++
+	—	—	—	+	+++	+++	+	+	—
+	—	++L	—	—	+	+	+	+++	++
+	—	+++	+++	++	+	+++	+++P	+++	++
—	—	+++	—	+++S	+	++	+++P	+++	++
No tuberculous changes									
+	—	++	+++	—	+	+++	++	+++	++
+	—	+	++	—	+	+++	+++P	+++	+++
+	—	++	—	++	+	++	++P	+++	++
+	—	—	—	—	++	+++	+	++	++
+	—	++	+++	+++	+++	+	+++	+++	—
—	+	++	—	+++	+++	++	+++	++	—
+	+	+++	—	++S	+++	+	++	+++	—
+	—	—	—	+	+++	+++	—	++	—
—	—	+	+++	—	+	+++	++P	+++	+++
—	—	+	—	—	+	++	—	+++	++
—	—	+	—	—	+	++	+	++	+
—	—	—	—	—	++	++	++P	++	++
+	—	++	—	+++S	+	+++	++	+++	++
—	No tuberculous changes								
—	—	—	—	—	+++	+	+	+	—
+	+	+++	+++	+	+	++	—	++	—
+	No tuberculous changes								
—	—	—	—	—	+++	++	+	+	—
+	—	+++	—	+++S	+	++	+++P	+++	++
+	—	++	+	+++S	+	++	+	+++	—
—	No tuberculous changes								
+	—	++	—	++S	+	+	+	+++	++
+	—	++	—	+	+	+++	+++P	+++	+++
—	—	++	++	+	++	++	+	++	+
—	—	++	—	++	+++	++	+	+++	+
—	No tuberculous changes								
—	No tuberculous changes								

(Conten.)

No.	Macroscopical Findings	Duration of Treatment	Sputum	Specimen
17.	Atelectatic upper lobe with numerous foci. Middle lobe with large cavities. Apical foci in lower lobe	20 days	—	Wall of cavity Tubercles of lower lobe Caseous gland Hilus gland
18.	Thumb-sized cavity in posterior segment of upper lobe. Tubercles in middle lobe	10 months	+	Wall of cavity Tubercles Hilus gland
19.	Upper lobe and apical segment of lower lobe partly atelectatic. Several cavities	11 months	—	Wall of cavity Parenchyma of upper lobe
20.	Upper lobe with large cavity. Whole lung shrunken. Atelectatic lower lobe	48 months	+	Wall of cavity Atelectasis of lower lobe Hilus gland
21.	Fibrotic and atelectatic upper lobe. Obstructed bronchus	6 months	—	Atelectatic tissue Bronchial ectasy Bronchus Hilus gland
22.	Apical segment of lower lobe with plum-sized cavity. Fibrotic pulmonary tissue	10 months	—	Tubercles I Tubercles II
23.	Upper lobe with cavity. Whole lung fibrotic with numerous foci	7 months	+	Wall of cavity Tubercle of anterior segment Hilus gland
24.	Fibrotic upper lobe with cavity in the apex	6 months	+	Wall of cavity Parenchyma of upper lobe Hilus gland
25.	Shrunken upper lobe with bronchial ectasies and cavity. Foci in apical segment of lower lobe	15 months	—	Upper lobe Middle lobe Hilus gland
26.	Atelectatic shrunken middle lobe	24 months	—	Middle lobe tissue Bronchus Hilus gland
27.	Lung with numerous small foci with cavities	8 months	+	Wall of cavity Tubercles of lower lobe Hilus gland
28.	Perforated cavity in pleura of upper lobe. Rice-like foci in upper lobe	10 months	—	Wall of cavity Tubercles of upper lobe Hilus gland
29.	Shrunken upper lobe with cavity. Apical segment of lower lobe atelectatic with foci	7 days	+	Wall of cavity Tissue of apical segment
30.	Plum-sized cavity in upper lobe. A few cavities in apical segment of lower lobe	12 months	+	Wall of cavity Basal wall of cavern Hilus gland
31.	Large cavity in apical segment of upper lobe	6 months	—	Wall of cavity Hilus gland
32.	Wholly fibrotic lung with cavities in shrunken upper lobe	6 months	+	Wall of cavity Tubercles of lower lobe Hilus gland
33.	Tuberculoma in upper lobe and apical segment of lower lobe	15 months	+	Wall of cavity Hilus gland
34.	Large cavity in upper lobe	15 months	+	Wall of cavity Inactive focus Hilus gland

Culture	Pneumonia	Inflammatory infiltration	Cavity	Necrosis	Tubercles	Epithel-Cells	Giant Cells	Fibrosis	Influence
−	−	+	++	+	++	+	−	+++	−
−	+	+++	−	+	++	+	+	+	−
−	−	+++	−	−	+	++	+	+	−
−	−	−	−	−	+	+	−	++	−
+	−	++	+++	++	+	+++	+++P	+++	++
−	−	++	−	+	+	++	++P	+++	++
−	−	−	−	−	++	+++	++P	++	++
−	−	+	+++	−	+	+	++P	+++	++
−	−	++	−	−	+	+++	++P	+++	++
+	−	++	+++	+++	−	+	+	+++	−
+	−	+	−	+	+	+	+	+++	−
+	−	−	−	+	+++	++	+	+	−
−	No tuberculous changes								
+	No tuberculous changes								
−	No tuberculous changes								
−	No tuberculous changes								
−	−	++	−	+++	+	++	++	+++	+
−	No tuberculous changes								
−	−	+++	+++	+	+++	+++	++	+++	−
−	+	+++	+	++	+++	+	+	+++	−
−	−	−	−	−	+++	+++	−	++	−
+	+	++	+	+++	+++	++	+	++	−
+	+	++	−	++	++	+	+	++	−
+	−	−	−	+	+++	+++	++	+	−
+	+	++	−	++	++	++	+	++	−
+	−	++	−	++	+	+	+	++	−
+	−	−	−	+	+++	++	−	+	−
+	−	++	−	+	++	+++	+++P	++	++
+	−	++	−	−	−	++	++	++	++
+	No tuberculous changes								
+	−	++L	+++	+++	+++	+++	+	+++	−
+	+	++L	−	++	+++	++	++	++	−
+	−	−	−	++	++	++	+++	+	−
+	−	+	++	++	+	++	++P	+++	++
+	−	+	+	++	+	+++	++P	+++	+++
No preparations									
+	+	++L	+++	+	+++	+	+	++	−
−	−	+	−	+	+++	++	++	+++	−
+	−	+	+++	++	+	+++	+++P	+++	+++
+	−	+	+++	++	+	++	++P	+++	+++
−	−	−	−	+	+	+++	+P	+++	++
No preparations									
No preparations									
−	+	++	+++	+++	+++	+++	++	+++	−
−	+	++	−	++S	+++	++	++	+++	−
−	−	−	−	−	+++	+++	+	++	−
−	−	++	+++	+++	++	+	+	+++	−
−	No tuberculous changes								
+	−	+++L	+++	+++	+	+	++	+++	+
−	−	++L	−	++	+	+++	+++P	+++	++
+	−	−	−	+	++	+++	+	+	−

L = A noticeable occurrence of polymorphonuclear inflammatory cells
S = solid
P = metaplastic giant cells

RESISTANCE COMPARED WITH THE INFLUENCE OF MEDICAL TREATMENT ON THE BASIS OF HISTO-PATHOLOGICAL FINDINGS

Table 9 shows results of resistance determinations compared with the influence of medical treatment in the light of histological findings. The duration of chemotherapy and the results of sputum examinations are included.

TABLE 9

THE RESISTANCE OF BACILLI COMPARED WITH THE DURATION OF CHEMOTHERAPY, THE RESULTS OF SPUTUM EXAMINATIONS, AND THE INFLUENCE OF CHEMOTHERAPY EVALUATED BY HISTOLOGICAL EXAMINATIONS

No.	Duration of Treatment	Sputum Staining	Preparation	Strepto-mycin	INH	PAS	Influ-ence
2	6 months	—	Wall of cavity	+	++	+	+
7	15 months	+	Wall of cavity	+++	+++	+	—
			Focus of lower lobe	+++	+++	+	+++
			Hilus gland	+++	+++	+	—
			Bronchus of lower lobe	+++	+++	+	++
8	12 months	—	Wall of cavity	+++	R	+	++
9	24 months	+	Wall of cavity of lower lobe	+	++	R	++
			Wall of cavity of upper lobe	+	++	R	+++
			Focus of lower lobe	+++	+	R	++
10	12 months	+	Wall of cavity	+	+++	R	—
			Middle lobe	+	+	R	—
			Focus of lower lobe	+	+++	R	—
			Hilus gland	+	+	R	—
12	13 months	+	Tuberculoma	R	+++	R	++
15	4 months	+	Tuberculoma	+++	+++	+++	++
			Tubercles	+++	+++	+++	+++
20	48 months	+	Wall of cavity	++	R	+	—
			Atelectasis of lower lobe	+	+	R	—
			Hilus gland	+	+	R	—
24	6 months	+	Wall of cavity	+	+	+	—
			Parenchyma of upper lobe	+	+	+	—
			Hilus gland	++	+	+	—
25	15 months	—	Upper lobe	++	+	++	—
			Middle lobe	++	++	+++	—
			Hilus gland	++	++	++	—
26	24 months	—	Pulmonary tissue	+++	R	+++	++
			Bronchus	+++	R	+++	++
			Hilus gland	++	R	++	++

R = Resistance

As can be seen in Table 9, all tubercle bacilli were sensitive to at least one drug. Specimens taken from different sites occasionally revealed a different resistance, the fact already pointed out by Canetti, and it seems likely that the occurrence of resistance is not dependent on the site of the specimen (cavity, another focus, lymphatic node). In comparing resistance of bacilli and histological reaction with specific medical treatment high sensitivity of bacilli was found to correspond to the favourable influence of medical treatment.

DISCUSSION

The material consisted of 34 patients with pulmonary tuberculosis whose resected lungs were examined bacteriologically and histologically. All patients were treated with antibiotic drugs for a long time. In addition, about two-thirds of the patients were given collapse treatment. The bacteriological examination revealed that in spite of collapse and specific medical treatment, more than half of the patients still excreted tubercle bacilli in sputum. Each patient had at least once shown a positive culture result from sputum. The following sites of resected lungs were examined bacteriologically: the main focus of the disease (usually the wall of the cavity), some other focus and a gland from hilus. The examination revealed that tubercle bacilli could be found in about 50 per cent of the tissue specimens cultured. In eight cases with microscopically negative sputum the bacilli were established by the cultivation of a tissue specimen while in three cases with positive sputum no tubercle bacilli could be found in cultures. The occurrence of tubercle bacilli in sputum and tissue does not seem to have clear correlation. Positive culture results from the main focus were most frequent. This may be due to the fact that there are more destroyed tissues in more extensive lesions combined with simultaneous circulatory and nutritional deficiencies. Thus it is not always possible to cause a sufficient concentration of the drugs, *e.g.*, in the cavity. — Resistance determinations were performed from foci of 11 patients. Among these patients, the strains were sensitive to all three or at least to one of the three drugs. There were differences in resistance of strains isolated from different foci of the same patient. Clear relationship could not be observed between the development of resistance and the duration of specific antibiotic treatment. The same result was obtained by Auerbach *et al.*

When examining histological tissue specimens attention was especially paid to the microscopical picture, in general. Special attention was also paid to the occurrence of pneumonias, the amount of perifocal inflammation and fibrosis, and the appearance of tubercles and specific cellular metaplasias. On the basis of these criteria, the influence of medical treatment on the process of lung was studied. Favourable influence was found in about 30 per cent, and less favourable in about 10 per cent. No influence could be established in about 60 per cent. None of the three groups showed exceptionally favourable reaction. Tubercle bacilli being sensitive to antibiotics used the influence of the treatment was often favourable estimated histologically.

Besides bacteriological observations, histological examination of tubercle foci seems to be valuable when the influence of specific medical treatment is evaluated. In addition, histological examination apparently gives some hints on the use of drugs in post-operative treatment.

SUMMARY

Bacteriological and histological investigations were carried out on 99 resected specimens of 34 patients with pulmonary tuberculosis treated with antibiotic drugs. Most specimens were taken from the main focus of the disease, from some other focus and hilus glands. Tuberculous and other ordinary bacterial cultures were made from the specimens, as well as histological preparations. In addition, from 28 specimens resistance to streptomycin, INH and PAS was established. Bacteriological investigations revealed the following facts: In spite of the combined medical treatment tuberculous tissue cultures were positive in about 50 per cent. Positive results obtained were most frequent from the main focus. Resistance to Streptomycin, INH and PAS also varied in different specimens of the same patient.

The favourable influence of antibiotic treatment could be established histologically in about 30, less favourable in about 10 per cent. No influence could be observed in about 60 per cent. The favourable influence of the treatment observed histologically and the susceptibility of bacteria occurred simultaneously.

The writers are of the opinion that histological investigation seems to be of certain significance when evaluating the influence of specific medical treatment.

REFERENCES

1. Auerbach, O.: Pathology of Tuberculosis as Affected by Antibiotics. Am. J. Surg. 1955:*89:*627.
2. Auerbach, J. O., Bernstein, S., Abbot, J., Wetrick, R. H., and D'Esopo, N.: The Pathology and Bacteriology of Lesions Resected two Years after Termination of Chemoterapy. Tr. 12th Conf. Chemother. Tub. 1953, 236.
3. Canetti, G.: Anatomical and Bacteriological Changes in Tuberculous Lesions under the Influence of Antibiotics and Chemoterapy. Bull. intern. Union ag. Tub. 1954:*24:*144.
4. Canetti, G.: Human Lung Tissue Reactions to the Tubercle Bacilli in Relation to Chemoterapy. Ciba Foundation Symposium on Experimental Tuberculosis. J. & A. Churchill Ltd London 1955.
5. Denst, J.: The Surgical Pathology of Isoniazid Treated Pulmonary Tuberculosis. Am. Rev. Tuberc. 1953:*68:*144.
6. Dubos, J.: Biochemical Determinants of Microbial Diseases. Harvard University Press, Cambridge 1954.
7. Auerbach, O., Hobby, Gladys I., Small, M. J., Lenert, T. F., and Comer, J. V.: The Clinicopathologic Significance of the Demonstration of Viable Tubercle Bacilli in Resected Lesions. J. Thoracic Surg. 1955:*29:*109.
8. Iwasaki, T.: Clinical and Pathomorphological Study on the Chemoterapy of Pulmonary Tuberculosis. Kekkaku 1955 30/Suppl. Ref. Experta Med. Sect. XV 1956:*9:*84.
9. Medlar, E. M., Bernstein, S. and Steward, D. M.: A Bacteriologic Study of Resected Tuberculous Lesions. Am. Rev. Tuberc. 1952: *66:*36.
10. Medlar, E. M.: The Behavior of Pulmonary Tuberculous Lesions. Am Rev. Tuberc. 1955:*71:*N:o 3 Part II.
11. Pätiälä, J., Turunen, M., and Brander, E.: The Significance of Tracheobronchial Lymphonodes in the Resection Treatment of Pulmonary Tuberculosis Ann. chir. et gynaec. Fenniae 1954:*43:* 229.
12. Sweany, Henry C., and Seiler, Hawley H.: The Pathology and Bacteriology of Resected Lesions in Pulmonary Tuberculosis. Dis. of Chest 1956:*29:*119.
13. Wallner, L. J., Thompson, J. R., and Lichtenstein, M. R.: Clinical and Histopathologic Study of Antimicrobial Therapy in Tuberculosis. Am. Rev. Tuberc. 1954:*69:*247.